Biopoly Money

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Patents and strong-arm tactics are helping make Affymetrix the Intel of biochips. Along the way, Affy wants to turn DNA into a proprietary system.

By Brian Alexander

They've got to be kidding. The entire corporate leadership of Affymetrix - maker of a DNA microarray known as the GeneChip, a device that may help determine whether I will be sexually potent, keep my hair, or bench-press 250 pounds at age 85 - wants to know why the company has attracted so much negative attention for its business tactics over the last several months.

For the past three hours, I've been sitting in a bland Santa Clara, California, conference room inside a generic concrete office block honeycombed with cubicles, listening to CEO Stephen Fodor, president Susan Siegel, executive vice-president Ken Nussbacher, CFO Edward Hurwitz, and general counsel Vern Norviel insist on how badly Affy is misunderstood - that they're just a bunch of good people trying to make a buck the Silicon Valley way, no different from Cisco or Intel. The executives feel put upon by pestering media, competitors, and academic critics who argue that tools like the DNA microarray should, in the name of progress, be made widely and cheaply available to researchers.

Somehow it's tough to sympathize. After all, it's not as though these executives are actually listening to their critics. They've exhaustively patented the technologies behind the GeneChip, and defended them aggressively with lawsuits, all in the name of owning the microarray market. What's more, the company has been amply rewarded for its bully tactics on Wall Street. Despite having generated only $96.9 million in revenues last year - and never having turned a profit - Affymetrix has seen its stock climb as much as 700 percent in 12 months.

Besides, I assert, Affy's situation isn't comparable to securing leadership in routers or semiconductors. This is an ethically contentious arena. What we're talking about are, ostensibly, the keys to the mysteries of all life on this planet. At the very least, the DNA microarray - a testing platform that will allow scientists to examine how genes in plants, animals, and humans are affected by just about any chemical or compound - should prove to be the most valuable biological research tool since the invention of the microscope. The small glass chips, printed with DNA material representing thousands of genes, can be subjected to every potential new drug, every component of food - anything that affects how genes work. This could change the very nature of scientific research. In short, I remind them, there's a lot at stake here.

Over the next month, this group of executives will have good reason to feel picked on. Six days from now, in the wake of a breakdown in talks intended to hasten cooperation between the publicly funded Human Genome Project - the effort to map every gene in the human body - and the private effort of a company called Celera to do likewise, President Clinton and British prime minister Tony Blair will declare that genetic information - the blueprint of life - belongs to everybody.

Their mid-March pronouncement will receive global media coverage, incite a rancorous debate about whether human genes can be proprietary corporate information, and decimate the market value of any company hoarding such data (sending Nasdaq's Biotech Index into a 300-point freefall well before the rest of Nasdaq followed suit). While Affy doesn't generally patent genes - but rather, the tools that enable gene research - the company will be taken along for the ride. Then, three weeks later, Affymetrix will lose part of an important lawsuit filed in a UK court by a renowned British scientist using a page out of Affy's own litigious playbook - a judgment that could spell real trouble for the company. Affymetrix execs will swear they'll appeal. But still, these two events will send the firm's market cap tumbling. While researching this story, I will watch Wall Street rip more than 70 percent out of the company's valuation - from $8.1 billion to $2.4 billion.

From an investor's perspective, it's been a tough first quarter. And such swings are precisely what make biotech a dangerous, and exhilarating, vehicle for businesses and investors alike. It's a chaotic place - equal parts promise and risk - subject not only to cutthroat competition but to a wild-card factor, as well: emotionally charged public attention. Add in the arcane nature of the business, which means, frankly, that most investors don't know what they're buying, and the smallest piece of news can send everyone scurrying. On one hand, then, Affy's fate depends on the same classic challenge as Cisco's: execution of a market-control strategy. On the other, not at all. Biotech isn't information technology.

The assembled officials know all this, of course. Every soon-to-be-public biotech company makes these arguments in the risk-assessment portion of their SEC filings. But today, the Affymetrix chorus unanimously disagrees with the suggestion that biotech is different. Business is business, they say, and in a booming microarray market, it takes aggression to seize opportunity. The company came to the marketplace first and shored up its patents. These executives did everything right, and the microarray now belongs to Affymetrix. Period. "People are assuming this is going to open up," executive vice president Nussbacher says of the array business. "We are fighting very hard to keep that from happening. We don't think it should."

In other words, Nussbacher is suggesting that anybody hoping to come into the array business (for now, Affy is the only company shipping product in any real volume) had better pay homage, and a lot of licensing money, to Affymetrix - or continue to face lawyers swinging Louisville Sluggers issued by the US Patent and Trademark Office. What Nussbacher doesn't realize is that his swagger scares people - it's the type of attitude that attracts the negative attention this group is complaining about.

But in the days before the carnage on Wall Street and in the courtroom, Affy's CEO may be getting the message. Fodor knows we're talking about a delicate subject: a technology that could lead to scent triggers tempting you to buy perfume at $135 per ounce, corn that prevents osteoporosis, or even a cure for breast cancer - and this kind of stuff touches a public nerve. Affymetrix has to be cautious, especially in the presence of a reporter. Fodor cautions Nussbacher: "We have to be careful not to project that image."

Behind the Zipper

To understand the GeneChip and the business around it, you need to understand a bit about microarrays in general. To get there, you have to know a little bit about DNA. Start by looking at your zipper. Think of it as the DNA double helix. Now unzip it. One side of the zipper - including one tooth, and the fabric that holds that tooth in place - is the rough equivalent of a basic unit of DNA, known as a nucleotide. The tooth is one of the four chemical bases that make up DNA: guanine (G), adenine (A), thymine (T), and cytosine (C).

Each tooth wants to mate with a tooth on the other side of the zipper, but these bases are picky: T will stick to A, and G will stick to C. When a base from one side finds its mate on the other side, they form a base pair and (OK, zip up - slowly) the DNA double helix is re-formed.

The union of enough of these base pairs constitutes a gene. Variations in the arrangement of the pairs will create different genes. In all, about 3 billion base pairs make up the estimated total of 100,000 human genes.

The 100,000 human genes c ntain ab ut 3 billi n base pairs. Previ usly f rced t sort through those pairs ne r tw at a time, researchers can n w use microarrays for mass testing.

Differences in base pairs make some people tall, or blond, or prone to tumors. Abnormal changes in these base pairs, called single nucleotide polymorphisms, or SNPs, might be the root causes of most noninfectious human diseases, including cancer, diabetes, and cystic fibrosis. Right now, nobody knows how many SNPs exist, but arrays will help geneticists zero in on them.

A microarray - also known as the biochip, the DNA chip, and a host of other trademarked names belonging to Affy competitors - is actually a simple, passive device. It's merely a tiny glass square onto which the company places one side of the unzipped nucleotides in a known position. These nucleotide "probes" are then washed with a test sample of an unzipped and specially marked strand of DNA derived from, say, a cancer patient's blood.

The unzipped nucleotides in the sample will find mates with unzipped probes on the chip. If a scientist is looking at, for example, a cancer-related gene on Affymetrix's P53 array, he will observe how bases from cancer DNA differ from mates with the probe DNA. Through this process (called hybridization, a version of which was patented in 1987 by a Yugoslavian scientist named Radoje Drmanac), scientists can literally see how normal nucleotides turn into cancer causers.

Like almost everything else about them, even the origins of microarrays are contested. Most agree that Oxford University professor Edwin Southern, the originator of the Southern Blot, an early DNA sequencing technique, was the first to come up with the principles behind the microarray. He applied for patents on his concepts in the UK in 1988. Those patents are now well-known, and are widely referred to as the Southern Patents.

The years that followed brought several different manufacturing methods from various teams of researchers. In 1991, a team led by Fodor, who was at the time working at the Affymax Research Institute in Palo Alto, California, published a paper in *Science* describing the creation of a microarray based on the same photolithographic technology used in the manufacture of computer microchips. Later, a team at Stanford University developed a new method - an early version of the spotted array technique - by depositing minuscule spots of DNA onto a glass slide via a method similar to offset printing, with the DNA material serving as the ink. A few companies, like Caliper, are now making arrays using microfluidics, running the chemistry through channels a few microns wide.

Deep Impact

To get an idea of how important the microarray is, consider the Human Genome Project. When project researchers finish their work sometime in the next couple years (the rival effort by the Celera unit of PE Corporation announced in early April that it had completed the mapping of the genome of a human being), they will have realized the approximate location of the genes and found most of the letters that make up those genes. But that's a far cry from knowing the precise order of the letters - much less what the letters, in conjunction, really say.

In effect, researchers will have pulled up to an empty library and dropped a load of billions of As, Cs, Gs, and Ts in a chaotic heap. Until the microarray, scientists trying to make sense of the letters would have had to pick through that heap a few nucleotides a time. Now they can work on a mass scale: For the first time, researchers have a printing press onto which they can load their letters

and publish complete books.

The financial implications of this development are obvious to everybody in gene research. Already, pharmaceutical companies - eager to cut the long odds (about 10 to 1) of successfully bringing a drug to market - have begun gobbling up all the genetic data they can find so that their drugs can be tailored more precisely. Some of the companies rocketing the Nasdaq to new heights earlier this year - Celera, Incyte, Hyseq, Human Genome Sciences - have been catering to that new hunger by building huge data banks of proprietary letter sequences, then selling access to that information.

Typically, if a drug company finds a sequence useful in the creation of a drug, genomics firms will receive royalties for the use of their patented data. This "reach-through" payment scheme - the ability to make money at both the front and back ends of drug development without exposure to the vagaries of drug testing and approval - is one reason why shares of these genomics companies soared in the first place. It also explains why investors panicked at the slightest hint of possibility that the rights of genomics companies to patent gene sequences could be questioned.

But, unlike genomics companies, Affymetrix doesn't usually patent sequences; it simply provides a testing platform for sequences. With a GeneChip, scientists can test a given compound on many sequences at once. They can see the results in hours - instead of days or months - and use those results to pinpoint promising compounds for further development, or to steer clear of dead ends.

The payoff for array makers could be huge, thanks to the research money that's chasing good tools. Pharmacia & Upjohn alone spent about $1.4 billion on R&D in 1999. Multiply that by what's spent by every other large drug maker, every agribusiness looking to make a new breed of superfood, and every corporation frantically searching for the genetic basis of everything from chocolate cravings to what makes roses smell the way they do, and the market for biochips seems limitless.

Amazingly, these applications might be just the beginning. The big payoff, say microarray experts, will be in analyzing single nucleotide polymorphisms and the rogue disease-causing proteins those SNPs create. SNP analysis will usher in the day of pharmacogenomics - custom drugs that treat each person's mutations. And in about a decade, experts maintain, physicians - and even parents with children home sick from school - will possess handheld microarray devices capable of revealing whether Susie's sore throat is a strep infection, and if so, which strain. Today, that very process involves taking a throat culture and waiting days for lab results.

According to several executives at companies hoping to compete for the microarray market, this has the potential to be a $10 billion-a-year industry within a decade. To put that in perspective, that's more than five times the total annual sales of Epogen, Amgen's blockbuster bioengineered treatment for anemia. In short, Affymetrix is in the fortunate position of selling most of the hammers to the construction companies at a time when there's a whole lotta building going on.

The financial implications of microarrays are obvious - and huge - to anyone in gene research. Biochips promise to become a $10 billion-a-year industry within a decade.

Bio-Bubbles

And Affymetrix has already sold a lot of hammers. The company's shipment of some 100,000 GeneChips in 1999 reflects its position as the only microarray company to fully commercialize its product for a hungry marketplace - while would-be competitors are still in the beta-testing phase. Affy's revenues nearly doubled in 1999. Net losses - attributable to research and development as well as to costs associated with ramping up mass production - dropped to $1.02 a share last year, from $1.11 a share in 1998. CFO Hurwitz says he's expecting Affy's first profit in the fiscal fourth

quarter of this year.

Do numbers like these justify that 700 percent run-up in Affy stock? Hardly. But there's a feeling that the GeneChip system has already become pervasive within both the pharmaceutical industry and academia. ("Everyone has an Affy," says Eric Neumann,vice president of life science informatics for Third Millennium, a Cambridge, Massachusetts-based consulting firm.) Which is more than enough for money-gorged Net-stock investors who - done with ecommerce plays - have set off in search of the next big thing. The Affymetrix situation has, in turn, inspired an onslaught of initial and secondary public offerings from competitors, thus creating a good old-fashioned Wall Street feeding frenzy for the stocks of any company even close to Affy's space.

Of course money managers have seen all this before. Ten years ago, a biotech stock bubble sent valuations soaring. Back then, investors didn't realize how much time and money are spent between research and actual development. Sure, there were a couple high-profile successes, like synthetic human growth hormone, but the returns couldn't justify the big financing - and the burst was so pronounced that investors stayed away from the industry for the better part of a decade. "I was in the middle of all that," says Rick Johnston, the man who runs Incyte's microarray research and manufacturing facility in Fremont, California. "There was an interest in biotech because it held all this promise. But ultimately, it left a sour taste in the mouths of investors."

This time it's different, Johnston argues. In fact, he says, today's excitement is about the fulfillment of those decade-old hopes. That is, it has simply taken this long to effectively use the innovations of those early days. Techniques like automated gene sequencing, polymerase chain reaction (which makes many copies of sequences), and sequencing via hybridization are now foundation technologies that enable the new genomics revolution - and they all contribute to the technology of microarrays, the tool that may make this revolution real.

R cky Beginning

While Affymetrix is in a prime position to benefit from the renewed interest in biotech, how the company fares may depend on its ability to wade through its current legal morass and cope with pricing and manufacturing woes. The seeds of these troubles were planted when the company was an amorphous Netherlands-based research firm called Affymax, founded in 1988 by Alejandro Zaffaroni, the Uruguayan entrepreneur who brought us the nicotine patch. Affymetrix spun out of Affymax in 1993 on the strength of Fodor's idea to use photolithography manufacturing to cram many nucleotide probes onto a small chip. The idea was brilliant, but it was also a trap.

Photolithography, in effect, plugged Affymetrix into Moore's law by allowing the steady increase in the number and density of nucleotides on each chip, thus reducing the manufacturing cost per probe. But increasing the number of nucleotide probes makes the chips themselves expensive and difficult to manufacture.

The process involves coating each chip with a photoreceptive chemical, laying down thousands of probes, and using 70 separate light masks to selectively activate a probe pattern. Probes not exposed to light remain inactive. Probes hit by light become active and usable for testing. Gaps between the probes measure a mere 100 angstroms - roughly the space occupied by 66 hydrogen molecules - which requires the manufacturing process to be perfect, lest a researcher end up looking at the wrong probe.

Partly due to the potential for mistakes, many of the probes are actually redundancies - checks put in place to ensure the researcher is testing what he thinks he is. Even with these safeguards, says Jonathan Aschoff - an investment analyst with Sturza's Medical Research, a financial analyst firm specializing in medical and biotech companies - up to 50 percent of the chips Affy makes fail the company's own quality control inspection. As recently as last year, another 20 percent of those that

actually shipped would still fail upon arrival, according to Affymetrix's biggest customer, Gene Logic.

Coupled with insufficient manufacturing capability, that kind of inefficiency translated to a 70-day order backlog last year. Of course Affy is aware of these problems. Company officials insist quality is improving - the post-QC failure rate is down to the single digits, they say. What's more, now that the Sacramento, California, manufacturing plant is running, chips are sometimes shipped within days of an order.

On the road to maximizing manufacturing efficiency, Affymetrix has also learned a thing or two about pricing. At first, the company mimicked the reach-through method employed by gene data-bank companies - but it became clear that the scheme was not a good fit. "When we started out, we were trying to price the product low so that when we sold the chip, we got a downstream drug royalty," recalls Norviel. "We quickly figured out that wouldn't work."

For one thing, with high up-front costs of its own, Affy couldn't afford to wait for royalties. Besides, big pharmaceutical companies objected to giving Affymetrix a cut of sales. So Affy decided to charge a bundle for its chips - anywhere from $100 to $2,000 each.

Big pharma undoubtedly felt the effects of that restructured pricing plan. Any given experiment will likely require not only several chips but also a machine (in Affy's case a laser scanner) to read the results, and computer equipment and software to interpret data. The package just to get started, according to Affy officials, is generally about $188,000. Tack on the price of several experiments and that number quickly jumps north of $250,000.

> **Today's applications are just the beginning. Coming up: Handheld arrays that test if a sore throat is a strep infection, and "pharmacogenomics," personalized disease-treating drugs.**

Given those numbers, it's easy to see why the new pricing structure hit the typically resource-starved academic researchers hardest - and they reacted in differing ways. Some offered to share intellectual property rights in return for chip discounts, according to Nussbacher. Others balked, believing such sharing would lead to restrictions on an academic's right to publish results of experiments and to profit from discoveries.

In a statement issued to researchers last June, the University of California made it clear that the Affymetrix supply agreement "impacts ... on your intellectual property rights and your ability to share research results relating to your use of Affymetrix chips or data resulting directly from chip use." In fact, according to the UC statement, "Because of the long period for which Affymetrix has some rights to inventions, you may need to consider the implications to future research sponsors of the potential reach of Affymetrix intellectual property rights."

Fodor emphatically denies the insinuation - that his company has reach-through in the academic community. An academic access agreement addendum Affymetrix supplied to *Wired* mostly supports his assertions, though it does contain several restrictions on the use of GeneChips and data.

Fodor says the company's rights to any researcher's inventions are extremely limited. The terms of the agreement, he argues, are such that if a GeneChip helps a researcher discover new nucleotides, Affymetrix has the right to negotiate a license to include them on its chip-array products. "We did negotiate reach-through with one university and a specific researcher, and it just came back and bit us," Fodor acknowledges. "We dropped the whole thing, but it was a black mark that took a long time to wear off."

Unleash the Lawyers

The resentment that has built up around Affymetrix - for its pricing structure as well as the stalled manufacturing process - tilled the soil for competitors. At first, the challenges bubbled up from scientists who realized they could make their own arrays with the Stanford-style spotting technology. Stanford professor Patrick Brown even established a Web site and discussion group that provided detailed instructions, drawings, and advice on how to do it.

The "roll your own" movement caught on. So much so that Affymetrix acquired Genetic MicroSystems of Woburn, Massachusetts, a manufacturer of array spotting systems, to cater to the growing faction.

Next came competition from Affy clients and partners frustrated by their lack of control. A nasty outbreak of lawsuits erupted, including one that could mean life or death for Affymetrix.

In 1997, Incyte was looking to gather more data for its library and perform experiments for corporate subscribers. The company considered buying Affy's GeneChips, says Johnston, but opted instead to purchase a small chipmaker called Synteni, which had sprung out of the Stanford array effort. Synteni's contact printing technology resulted in dense - and cheaper - arrays. Though Incyte used the chips only internally, Affymetrix sued, claiming Synteni/Incyte was infringing on its chip density patents. The suit argues that dense biochips - regardless of whether they use photolithography - cannot be made without a license from Affymetrix.

Incyte countersued and has since filed suit against genetic database competitor Gene Logic for infringing Incyte's patents on database building. Meanwhile, Hyseq sued Affymetrix, claiming infringement of nucleotide hybridization patents obtained by its chief scientific officer, Radoje Drmanac. Affy, in turn, filed a countersuit, claiming Hyseq infringed the spotted array patents. Hyseq then reached back and found an additional hybridization patent it claimed that Affy had infringed. Hyseq is suing for four patents - all of which involve the nucleotide hybridization patent obtained by Drmanac.

Many in the industry seem to feel that Affy's claims are outlandish. It's as if, they say, upon producing the first Model T, Henry Ford had tried to gain the rights to the very idea of the automobile, and obstructed anyone who tried to develop anything with four wheels. "Affymetrix is certainly trying to leverage a proprietary position," says Paul Boni, who until recently was an analyst with Punk, Zeigel & Company. Incyte general counsel Lee Bendekgey says the suits are a matter of "whether what they invented covers all kinds of microarrays or whether it just involves a particular type of microarray manufactured using a particular process."

Norviel will have none of the obstruction argument. "That's what people who don't want to pay say," he counters, insisting that Affymetrix has an aggressive licensing policy that allows others to enter the market. "We have a standard licensing program. It's a two-page form. Most people rumple the pages a little bit, roll their eyes, and say, 'Oh, you are so expensive,' and then they sign. You don't get any of this foolishness."

To further its goal of becoming the standard array, Affymetrix has also tried to standardize the all-important data-handling steps involved in interpreting array test results. In late 1997, Affy joined with Molecular Dynamics to form the Genetic Analysis Technology Consortium (GATC), a software standard designed to favor Affy hardware. Affymetrix now advertises its technology as GATC compliant, and, in an obvious effort to make GATC - and therefore the GeneChip - the standard, Affy's academic access agreement requires scientists to "make reasonable efforts to transfer data ... in accordance with the GATC standards group whenever possible." Not surprisingly, this move has ruffled feathers, too.

"GATC is not the most modern, up-to-date scheme," explains consultant Eric Neumann, noting that a new program called the Microarray Gene Expression Data Base is being developed in response to GATC so that results from multiple microarray technologies can be cross-analyzed. "It frees you from one vendor, and it's an open consortium ... Affymetrix can't have complete control of all the pieces. Nobody can."

It's this sort of controlling move that has led some in the industry to relish Affy's most recent - and most potentially damaging - legal battle, the fight with Edwin Southern. The firm Southern founded, Oxford Gene Technologies (OGT), filed suit against Affymetrix in June of last year, accusing the company of infringing the Southern Patents and attempting to obtain a license illegitimately. "Every array they make infringes the patent," says Chris Shelley, Southern's UK solicitor.

With an April 7 UK verdict coming down in favor of Southern, Affymetrix is on the spot. Yet its chances are good, Fodor says, because Affy's patents are ironclad and Southern's weak. Still, Affy was concerned enough about the Southern Patents back in 1998 to enter into negotiations with OGT to obtain access to them. In June of that year, Affy was about to agree to pay $20 million and grant OGT a cross-license in return for access to the Southern Patents. But fearful of letting OGT have access to its patents, Affy called off the negotiations in August.

Affy's market share, tight control, and pricing structure have built up strong resentment, and tilled the soil for competitors ranging from upstarts with new tech to manufacturing giants.

Instead, the company made a deal - Shelley called it a "ruse," and Justice Robin Jacob, the presiding judge in London, agrees - with Beckman Coulter, an instrument maker then licensed under the patents. Affy agreed to enter into a consortium with Beckman Coulter, or, if OGT refused to give the "consortium" a license, to buy Beckman Coulter's embryonic array business for $5.9 million and throw in another $5 million of research work. In other words, Affymetrix would get access to the Southern Patents for almost half price.

Nussbacher explains the paradox of denigrating Southern's patents even while going through contortions to get at them: "There's a lot at stake with the market cap we have, and if you can mitigate that risk with a couple million dollars, we'll do it, sure."

The machinations may cost Affy more than "a couple million dollars." Affymetrix put up a fight over the Beckman Coulter deal because it said the license it obtained precluded any infringement of Southern's array patents. But the UK judge struck down the deal, so now Affy will have to prove - in the UK and in the US, where the case comes up in October - that it's not infringing. Even Fodor admits that this could be a problem. "It's not clear yet what the patent office is going to grant Southern. There's still a question whether or not the patents he's going to get will cover us."

Those familiar with the world of microarrays say the Southern Patents can't be brushed off. In fact, in December of last year, first Incyte and then Agilent obtained array licenses from Southern. "If we didn't think they were valid patents, we wouldn't have bought them," says Incyte's Lee Bendekgey.

Justice Jacob offered a solution in his summary. "In principle OGT [was once] willing to grant a license to Affymetrix. Indeed, they probably still are. Notwithstanding the fact that they have started infringement proceedings, there may be a negotiated outcome, including a license."

So Affymetrix may find itself in a cross-licensing deal after all. Indeed, it may have no choice. If it refuses and loses on appeal, Southern's solicitor Shelley says, "OGT can close [Affymetrix] down."

Big C mpetition

While a shutdown at the hands of OGT seems unlikely, Affymetrix still could be headed for a rough patch. Many say the biochip segment is taking the path of microprocessors, with a tumultuous legal beginning followed by licensing and niche marketing. But Affymetrix is trying to throw a wrench into the works. "Semiconductors were in this position for 10 or 15 years, and that got sorted out," Hyseq president and CEO Lewis Gruber says of the mess. "It's not that we're behind the curve in rationalizing markets and cross-licensing. But you have a strong resistance on the part of Affymetrix to doing anything of that sort. They have relied on telling people they are - and will be - the only chip on the market."

This posture has done nothing to put more arrays into the hands of the people clamoring for them (Harvard professor George Church says it has been "pathological to research"), a fact that has spurred even more competition. "The people who need to use the stuff, both pharmas and the academic community, don't like infighting," Neumann explains. "They want to see results."

So companies like 3M, Agilent, Motorola, Corning, and Hitachi - none of whom are intimidated by Affy's patent portfolio - as well as a host of small players are lining up to break Affymetrix's hold on the market. Every new entry has formed one or more alliances with pharmaceutical and equipment companies who are themselves often signed up with several different array makers. "This is just unbelievably dynamic," says Incyte's Johnston. "It's tough to know who to bet on. I don't think you can bet on any one technology. If you look at big pharma, they're at the roulette table, just putting bets everywhere."

PE Corporation illustrates that point. PE, parent company to Celera, has acquired Third Wave, an SNP detection company based in Madison, Wisconsin; it also provides mass spectrometry equipment to another SNP analysis firm, Sequenom, of San Diego; and it collaborates with Hyseq. PE is also working with 3M to develop 3M's array and has put up $5 million to finance Illumina, a San Diego array company.

Affy is also at risk from smaller upstarts. Illumina is using licenses from Tufts University to mount micron-scale beads with attached nucleotides into the tips of optical fibers. And it employs Mark Chee, an array inventor who worked with Fodor at Affy. Lynx, based in Hayward, California, is using beads that, according to company president and CEO Norrie Russell, can do gene-expression analysis on all 20,000 to 30,000 genes that a cell expresses. Financial analysts think the Lynx system, which BASF and DuPont are testing, could be a powerful competitor. The National Institutes of Health makes its own arrays - 5,000 last year - using print-spotting, and it's trying to develop new technologies to place in the public domain or license to the highest bidder.

But the biggest threat is coming from the industrial-scale manufacturers. Corning and Motorola plan to unveil platforms sometime this year. Nick Naclerio, formerly with Darpa and now VP and general manager of Motorola's new Biochip Systems, says Motorola will market high-density array technology that grew out of collaboration with Argonne National Laboratory. "We're developing arrays like Affy's or Incyte's or Hyseq's," he says, "but also microfluidic chips like Caliper's and new detection technologies." He says the chips work with an electronic detection process and that Motorola "can guarantee the quality of the probes going on the chip. Affy can't do that. We can."

It's the recently spun-off division of Hewlett-Packard known as Agilent, though, that's gone from being Affy's partner to its archenemy. In 1994, Affymetrix and HP struck a deal for HP to create an Affy-compatible confocal laser scanner to illuminate the fluorescently labeled nucleotides. Under the terms of the agreement, any customer who buys a complete system before 2003 gets a bundled HP/Affymetrix GeneArray scanner. But last winter Agilent announced it was going after the microarray business, a move that sent Affy executives back-pedaling on their partner's prowess. "HP has a big market in communications and all this other stuff," Fodor says. "How serious are they?"

Fact is, Agilent is further along the path to marketing a product than any of the other big players. To add insult to injury, it has linked with another former Affy customer, Rosetta Inpharmatics - a Seattle-area microarray firm that grew out of labs at the University of Washington - to create a high-density, inkjet-spotted array. Now Affymetrix finds itself in the awkward position of selling a competitor's scanners until 2003. "I guess we didn't expect this sort of behavior out of HP," Fodor says glumly.

HP spinoff Agilent may prove to be the biggest threat to the GeneChip's dominance. But users want arrays now, amid the rising genome data flood. The first mover has the advantage.

"They worked with us, and now they covet the space," Nussbacher adds, accusing Agilent of using Southern as a front to attack Affymetrix.

Knocking Affy off the Throne

No matter who gains footholds, the price of arrays is about to drop - a lot. Which is why Incyte president Randy Scott says he's "enjoying the entrance of Motorola, Agilent, and Corning." Neumann and Incyte's Johnson think microarrays will even soon be priced as "a commodity item."

Affy executives realize that prices will fall, but downplay the effect that will have on their business. "Our costs should drop at least as fast as our prices," CEO Edward Hurwitz says. "Our margins will be sustained or improved over time."

Affymetrix also has an impressive balance sheet, including $225 million in cash reserves as of December 31 and a still-sizable valuation, to buy its way out of an onslaught. Most likely, the company will drop Agilent when the scanner deal expires and make use of recently acquired instrument company Genetic MicroSystems.

Threats from innovations will be absorbed, too. "We're becoming a full-fledged operating company, and the way leading-edge companies stay that way is to go out and acquire and partner with technologies they can't invent," Hurwitz says. "Sit tight for the next 6 to 12 months and you'll see us make outright acquisitions and invest in the next generation of companies."

The only problem is that the big boys will shop, too. Which means Affymetrix could find itself in a bidding war against companies with annual revenues in the billions of dollars.

Ultimately, when it emerges from the battles of the next year or so, Affymetrix is likely to have fallen from its place as the Kleenex or Q-Tip of the array business. But that doesn't mean Affy is going away. As with most distracting corporate legal skirmishes, odds are that Affymetrix and Incyte will settle. The Hyseq stew appears to be on low boil, and while the Southern suit is a danger - even in what's likely to be a more conservative, Affy-friendly US court come October - the matter seems destined to result in some kind of cross-licensing arrangement.

Meanwhile, saying you can make arrays is one thing, but making them is another. Thus far, only Affymetrix has made microarrays in any volume for outside customers. In genomics, as in comedy, timing is everything. Users want arrays now, while the data flood from genome research spews. Many customers won't want to wait until the bugs are worked out of competing technologies.

Also, Affy's GeneChips win good reviews for the density of their probes and for the readability of their data, making them especially valuable for the niche that calls for big-picture looks at how genes turn on or off. Finally, Affymetrix is a known quantity, and some heavy investments have already been made by users reluctant to switch. The first mover has the advantage.

Just don't expect clear answers about winners and losers anytime soon. "It's all pretty nutty," laughs Robert Cohen, a consultant with Front Line Strategic Management, a Bay Area firm. "The genomics sector is driving a lot of the nuttiness. There are so many options, so many components and parts-making systems. It's all a bit dizzying."

"It will get worse before it gets better," agrees analyst Aschoff.

Meanwhile, the tension between commerce and the ethics of access to biotechnology miracles will continue to rise. "My personal view is that this field needs to be opened up," Edwin Southern says. "There are important and deep issues here that shouldn't be directed by narrow commercial concerns."

Of course Affymetrix cares about human betterment, company president Siegel says. But "it's not fair to our shareholders to just give up the technology. Everyone would love a piece of this pie - love to compete free and clear. Affymetrix has done a tremendous job of building up the patent estate, so we are an incredible target. People love to pick on us. We are viewed as an evil empire."

Indeed, if its business was IT, Affy would be revered. But at the end of the day, it's not - and that's something Affymetrix has yet to come to terms with.

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